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REDUCTION OF CARBONYL COMPOUNDS VIA HYDROSILYLATION

V *. SYNTHESIS OF OPTICALLY ACTIVE ALLYLIC ALCOHOLS VIA REGIOSELECTIVE ASYMMETRIC HYDROSILYLATION

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Summary

Regioselective asymmetric reduction of prochiral α,β-unsaturated ketones to optically active allylic alcohols was performed via hydrosilylation catalyzed by a rhodium(I) complex with (+)-BMPP, (+)-DIOP and (—)-DIOP as chiral ligands. The allylic alcohols with optical purity up to 69% e.e. were obtained in good yields. The extent of asymmetric induction was found to depend on the stereoelectronic matching of the chiral ligand, ketone and hydrosilane employed. In the asymmetric reduction of (*R*)-carvone, leading to carveol, the extent of asymmetric induction was found to depend markedly on the ligand/rhodium ratio. Either *trans*-(5*R*,1*S*)-carveol or *cis*-(5*R*,1*R*)-carveol was obtained with good stereoselectivity by using (—)-DIOP or (+)-DIOP as chiral ligand, and it turned out that the chiral center present in carvone had only a slight influence on the asymmetric induction by the chiral catalysts.

Introduction

The asymmetric reduction of carbonyl compounds via hydrosilylation catalyzed by chiral rhodium complexes have been studied extensively [1]. In the previous papers [2], we reported the highly selective 1,2- as well as 1,4-addition of hydrosilanes to α,β-unsaturated ketones and aldehydes by catalysis with tris(triphenylphosphine)chlororhodium. These regioselective reductions are applicable to the asymmetric synthesis of optically active ketones and allylic alcohols. Two kinds of regioselective asymmetric reduction of prochiral α,β-unsaturated ketones can be effected through 1,4-addition or 1,2-addition

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* For part IV see ref. 13.

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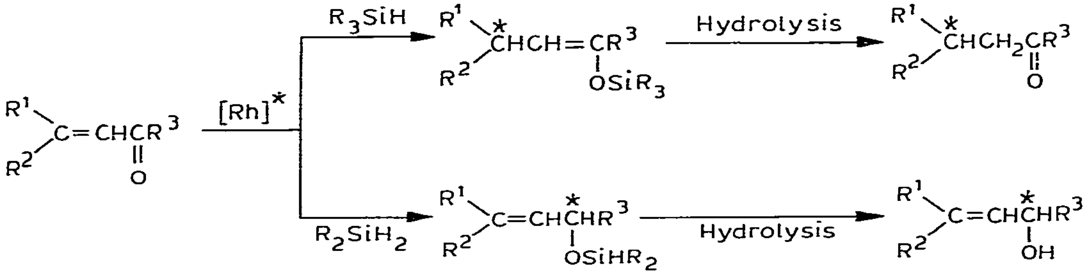
of hydrosilanes: the former reaction induces asymmetry on the β-carbon to give optically active ketones while the latter provides optically active allylic alcohols (eq. 1). In fact, Hayashi, Yamamoto and Kumada performed the asymmetric reduction of α,β-unsaturated ketones using the 1,4-addition, and obtained optically active ketones [3]. We describe here our study on the regioselective asymmetric reduction of carbonyl groups in α,β-unsaturated ketones, which gives optically active allylic alcohols [4].



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Results and discussion

Asymmetric reduction of prochiral α,β-unsaturated ketones to optically active allylic alcohols

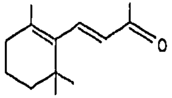
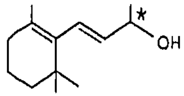
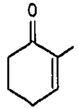
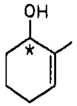
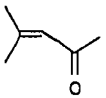
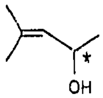
An α,β-unsaturated ketone was allowed to react with a dihydrosilane in the presence of a chiral rhodium catalyst (0.3—0.5 mol%) in benzene. The resulting silyl enol ether was desilylated with potassium carbonate in methanol to give the corresponding optically active allylic alcohols in high yields. β-Ionone (**1**), 2-methyl-2-cyclohexenone (**2**) and mesityl oxide (**3**) were chosen as typical substrates, and (+)-BMPP (BMPP = benzylmethylphenylphosphine), (+)-DIOP and (—)-DIOP (DIOP = 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) were employed as chiral ligands.

Results are summarized in Table 1. Optical purities of the resulting alcohols were determined on the basis of NMR spectroscopy using an optically active shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), [Eu(facam)$_3$]. In the case of **3**, however, the optical yield was determined for 4-methylpentan-2-ol which was derived from the silyl ether of 4-methylpent-3-en-2-ol (**6**) by hydrogenation and desilylation, since an attempted determination of the optical purity of **6** was unsuccessful (see Experimental). Although the absolute configurations of **4**, **5** and **6** are unfortunately not reported in the literature, they are predicted based on the results obtained so far in the asymmetric reductions of simple prochiral ketones catalyzed by rhodium complexes with DIOP and BMPP [1,12].

As Table 1 shows, the extent of asymmetric induction is very sensitive to the structures of the substrates and hydrosilanes when DIOP is employed as chiral ligand, which forms a sharp contrast to the results on using BMPP. This may be due to the fact that the stereoelectronic requirements in the coordination sphere of the DIOP-rhodium complex, which has a *cis* configuration, are quite different from those of the BMPP-rhodium complex, which has *trans* configuration.

TABLE 1

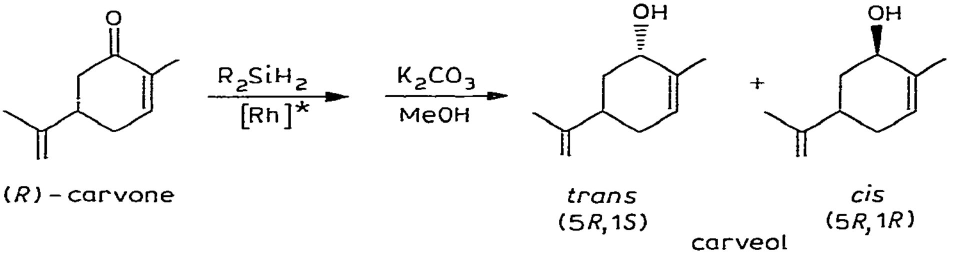
SELECTIVE ASYMMETRIC REDUCTION OF α,β-UNSATURATED KETONES

Substrate	Hydrosilane	Chiral ligand ^{d}	Conditions	Product	Yield (%)	$[\alpha]_D^{20}$ (neat)	Optical yield ^{a} (%)
 1	Ph_2SiH_2	(+)-BMPP	18–20°C, 2 h	 4	68	−0.98	21^{b} (*R*)^{e}
	α-$NpPhSiH_2$	(+)-BMPP	20–30°C, 4 h		71	−1.25	27^{b} (*R*)^{e}
	Ph_2SiH_2	(+)-DIOP	18–20°C, 20 h		70	+0.08	1.3 (*S*)^{e}
	α-$NpPhSiH_2$	(+)-DIOP	18–20°C, 20 h		72	+0.08	1.3 (*S*)^{e}
 2	Ph_2SiH_2	(+)-BMPP	18–22°C, 15 h	 5	68	+43.0	41^{b} (*R*)^{e}
	α-$NpPhSiH_2$	(+)-BMPP	18–22°C, 15 h		70	+45.0	43^{b} (*R*)^{e}
	Ph_2SiH_2	(+)-DIOP	18–20°C, 17 h		83	−20.8	15 (*S*)^{e}
	α-$NpPhSiH_2$	(+)-DIOP	18–20°C, 17 h		77	−70.6	52 (*S*)^{e}
 3	Ph_2SiH_2	(+)-BMPP	25°C, 8 h	 6	60	−1.42	$34^{b,c}$ (*R*)^{e}
	α-$NpPhSiH_2$	(+)-BMPP	10–30°C, 4 h		62	−1.44	$35^{b,c}$ (*R*)^{e}
	Ph_2SiH_2	(−)-DIOP	18–20°C, 20 h		60	−0.96	18 (*R*)^{e}
	α-$NpPhSiH_2$	(+)-DIOP	20°C, 40 h		58	+1.99	38 (*S*)^{e}

[a] Based on NMR analysis using $Eu(facam)_3$ as chiral shift reagent. [b] Optical yield is calibrated by the optical purity of (+)-BMPP (78% e.e.). [c] Optical yield was estimated for the hydrogenated product, 4-methylpentan-2-ol based on NMR analysis. [d] P/Rh = 3 (See Experimental section). [e] Predicted configuration.

Asymmetric reduction of carvone to carveol

It has been reported that the reduction of carvone with lithium aluminum hydride gave *cis*-carveol selectively (*cis/trans* = 94/6) [5,6] in accordance with "steric approach control" [7]; diphenyltin hydride reduction also gave *cis*-carveol in excellent selectivity (*cis/trans* = 97.1/2.9) [6] while the Ponndorf reduction gave *cis*-carveol in only slight excess [8,6]. On the whole, reduction of carvone with metal hydrides tends to give *cis*-carveol selectively. However, as far as we know, no report has been published on the reduction of carvone leading to *trans*-carveol selectively. Accordingly, it is of value to provide a convenient route to *trans*-carveol. From this point of view, we carried out the asymmetric reduction of (*R*)-carvone using rhodium catalysts with (+)-BMPP, (+)-DIOP and (—)-DIOP as chiral ligands (eq. 2). Results are listed in Tables 2 and 3.



(2)

As Table 2 shows, *cis*-(5*R*,1*R*)-carveol was obtained predominantly when (+)-BMPP or (—)-DIOP were used as chiral ligand whereas *trans*-(5*R*,1*S*)-carveol was the main product when (+)-DIOP was employed. As both (—)-DIOP-Rh and (+)-DIOP-Rh catalysts showed almost the same stereoselectivity, it appears that the chiral center at the C(5) position does not have any appreciable influence on the asymmetric induction in this system. At this stage, the best result giving *cis*-(5*R*,1*R*)-carveol was realized by using diethylsilane and (—)-DIOP-Rh (0.3 mol%) in benzene: 25° C, 24 h, 85% yield, *cis/trans* = 84.5/15.5 (69% asymmetric induction).

TABLE 2

ASYMMETRIC REDUCTION OF (*R*)-(—)-CARVONE [a]

Hydrosilane	Chiral ligand [d]	Conditions	Yield (%) [b]	$[\alpha]_D^{20}$ (neat)	Carveol (*R*,*S*)/(*R*,*R*) [b]	Optical yield (%)
α-$NpPhSiH_2$	(+)-BMPP [c]	20°C, 45 h	91	—74.2	29.0/71.0	42 [c]
Ph_2SiH_2	(+)-BMPP [c]	20°C, 13 h	95	—81.7	30.6/69.4	39 [c]
α-$NpPhSiH_2$	(+)-DIOP	20°C, 5 h	98	—161	77.4/22.6	55
	(—)-DIOP	20°C, 5 h	95	—62	20.9/79.1	58
Ph_2SiH_2	(+)-DIOP	20°C, 12 h	78	—134	62.1/37.9	24
	(—)-DIOP	20°C, 20 h	81	—92	37.3/62.7	25

[a] All reactions were run with 20 mmol of (*R*)-carvone and 24 mmol of dihydrosilane in the presence of 6.0×10^{-2} mmol (0.3 mol%) of rhodium catalyst in 40 ml of degassed benzene. [b] Determined by GLC analysis. [c] (+)-BMPP with 78% e.e. was used, but the optical yield is not calibrated by the purity. [d] P/Rh = 3 (see Experimental section).

TABLE 3

EFFECTS OF LIGAND/RHODIUM RATIO ON THE STEREOSELECTIVITY IN THE ASYMMETRIC REDUCTION OF (*R*)-CARVONE [a]

$\frac{[(+)\text{-DIOP}]}{[\text{Rh}]}$ [b]	Benzene (ml)	Carveol (*R*,*S*)/(*R*,*R*) [c]	Optical yield (%)
0.75	10	38.6/61.4	22.8
1.0	10	65.2/34.8	30.5
1.5	5	74.8/25.2	49.6
1.5	10	77.5/22.5	55.0
1.5	20	78.7/21.3	57.4
2.0	10	73.1/26.9	46.1
2.5	10	59.3/40.7	18.6

[a] All reactions were run with 5.0 mmol of (*R*)-carvone and 6.0 mmol of α-$NpPhSiH_2$ in the presence of 1.5×10^{-2} mmol of rhodium catalyst in benzene at 20°C for 20 h. Chemical yields (GLC analysis) were 95—99% in all cases. [b] $[Rh] = 1/2[Rh(COD)Cl]_2$ (COD = 1,5-cyclooctadiene). [c] Determined by GLC analysis.

It is of interest to note that the stereoselectivity of the present reaction was found to depend markedly on the ligand/rhodium ratio. As Table 3 shows, the most effective asymmetric induction, *cis*-(5*R*,1*R*)/*trans*-(5*R*,1*S*) = 21.6/78.4, was brought about with a molar (+)-DIOP/rhodium ratio of 1.5, while the stereoselectivity suddenly decreased to a *cis/trans* ratio of 40.7/59.3 with a (+)-DIOP/rhodium ratio of 2.5, and moreover, inversion of the preferred configuration took place with a (+)-DIOP/rhodium ratio of 0.75. The results seem to indicate that the most effective catalyst species for inducing *R* configuration is generated with a (+)-DIOP/rhodium ratio of 1.5, whereas other catalyst species, being not suitable to the induction of *R* configuration or even being favorable for the induction of *S* configuration, are formed when the (+)-DIOP/rhodium ratio is higher or lower than 1.5, although the structures of such catalyst species have not been clarified yet. It was also found that (i) the concentration of the reactants has little influence on the stereoselectivity, and (ii) the stereoselectivity does not change within experimental error from the beginning till the end of the reaction.

In conclusion, either *cis*-(5*R*,1*R*)-carveol or *trans*-(5*R*,1*S*)-carveol is obtained in good stereoselectivity via asymmetric hydrosilylation of (*R*)-carvone using a diethylsilane-(—)-DIOP combination or an α-naphthylphenylsilane-(+)-DIOP combination under suitable conditions; the selective formation of *trans*-(5*R*, 1*S*)-carveol is especially noteworthy, since the usual achiral metal hydrides cannot give this isomer as major product [5,6,8].

Experimental

Measurements

The boiling points are uncorrected. The nuclear magnetic resonance (NMR) spectra were recorded on a Varian HA-100 spectrometer, using TMS as the internal standard. Analytical gas chromatography (GLC) was carried out on a Shimadzu GC-3BF or GC-3BT using columns packed with 15% PEG-1000 on

Chromosorb W. Optical rotations were measured with a Union PM-201 degital polarimeter.

Materials

Dihydrosilanes were prepared from chlorosilanes by known methods. β-Ionone, 2-methylcyclohex-2-en-1-one, mesityl oxide and (*R*)-carvone were commercially available, and were distilled before use. [Rh-(1,5-cyclooctadiene)-Cl]$_2$ was prepared in accordance with the literature method [9]. (*R*)-(+)-Benzylmethylphenylphosphine ((+)-BMPP) was prepared in accordance with Mislow's method [10] using triethylamine as a base. The optical purity of (*R*)-(+)-BMPP was determined to be 78% e.e. based on the Horner's procedure [11]. (+)- and (—)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(+)- and (—)-DIOP] were commercially available from Strem Chemicals Inc. The shift reagent for NMR measurements, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(facam)$_3$] was commercially available from Willow Brook Laboratories Inc.

Preparation of catalyst solution

The optically active catalyst was prepared in situ by the reaction of [Rh(COD)-Cl]$_2$ (COD = 1,5-cyclooctadiene) with chiral phosphine in degassed benzene at ambient temperature. In a typical experiment, 10 mg (2.0×10^{-2} mmol) of [Rh(COD)Cl]$_2$ and 30 mg (6.0×10^{-2} mmol) of (+)-DIOP were dissolved in 5 ml of benzene under argon and stirred for 15 min. Similarly, the BMPP-rhodium complex catalyst was prepared from 10 mg (2.0×10^{-2} mmol) of [Rh(COD)Cl]$_2$ and 28 μl (1.31×10^{-1} mmol) of (*R*)-(+)-BMPP in 5 ml of benzene in a typical run.

Asymmetric reduction of β-ionone to β-ionol

A typical procedure is described for the asymmetric reduction of β-ionone using α-naphthylphenylsilane and (+)-BMPP.

To a 5 ml of degassed benzene solution of (+)-BMPP-rhodium complex (6.0×10^{-2} mmol, 0.3 mol%) was added a mixture of 3.85 g (20 mmol) of β-ionone and 5.64 g (24.1 mmol) of α-naphthylphenylsilane in 10 ml of benzene. The mixture was stirred at 18—20°C for 20 h at which point the reaction was complete. The progress of the reaction was checked by GLC and/or NMR analyses. To the reaction mixture were added 30 ml of methanol and 30 mg (2.1×10^{-1} mmol) of potassium carbonate. Methanolysis proceeded readily within several minutes. GLC analysis using n-octadecane as internal standard revealed that β-ionol was produced in 86.5% yield. The solvent was evaporated and the residue was submitted to column chromatography on silica gel, and (—)-β-ionol (2.78 g, 71.3%) was obtained. The NMR measurement using Eu(facam)$_3$ showed that the purity of the enantiomer thus formed was 34% e.e. For the measurement of optical rotation the obtained allylic alcohol was distilled under reduced pressure: b.p. 89°C/0.1 Torr, $[\alpha]_D^{20}$ —1.25° (neat).

Asymmetric reduction of 2-methyl-2-cyclohexenone to 2-methyl-2-cyclohexenol

Typically, in a manner similar to that described above, 3.33 g (30.2 mmol) of 2-methyl-2-cyclohexenone were hydrosilylated by using 8.44 g (36 mmol) of α-naphthylphenylsilane and the (+)-DIOP-rhodium catalyst (0.3 mol% based on the enone) in 20 ml of benzene. The silyl ether produced was methanolyzed and submitted to column chromatography on silica gel. 2-Methyl-2-cyclohexenol (2.47 g, 73%) was obtained as a colorless liquid, which was distilled further for the measurement of optical rotation, b.p. 70°C/12 Torr, $[\alpha]_D^{20}$ −70.6° (neat). The NMR measurement using $Eu(facam)_3$ determined that the purity of the enantiomer thus obtained was 52% e.e.

Asymmetric reduction of mesityl oxide to 4-methyl-3-penten-2-ol

In a manner similar to that described above, 5.89 g (60.0 mmol) of mesityl oxide were hydrosilylated by using 16.0 g (72.1 mmol) of α-naphthylphenylsilane and the (+)-DIOP-rhodium catalyst (0.3 mol% based on the enone) in 40 ml of benzene. After the reaction was complete, the solution was divided into two fractions by using volumetric flasks. Half of the reaction mixture was methanolyzed and submitted to a column chromatography on silica gel to give 4-methyl-3-penten-2-ol (1.93 g, 58%), which was distilled further for the measurement of optical rotation; b.p. 80°C/72 Torr, $[\alpha]_D^{20}$ +1.99° (neat).

The other half of the hydrosilylated mixture was stirred under an atmospheric pressure of hydrogen at ambient temperature for 72 h in the presence of tris(triphenylphosphine)chlororhodium (50 mg, 5.4×10^{-2} mmol) as a catalyst. GLC analysis of the reaction mixture showed that the hydrogenation was complete. Then the saturated silyl ether was methanolyzed and submitted to a column chromatography on silica gel to give 4-methylpentan-2-ol (2.03 g, 61%): b.p. 78°C/92 Torr, $[\alpha]_D^{20}$ +6.48° (neat). The NMR measurement using $Eu(facam)_3$ determined the optical purity of 4-methylpentan-2-ol thus obtained as 38% e.e.

Asymmetric reduction of (R)-carvone

Typically, in a manner similar to that described above, 3.00 g (20.0 mmol) of (*R*)-carvone were hydrosilylated by using 5.63 g (24.0 mmol) of α-naphthylphenylsilane and the (+)-DIOP-rhodium catalyst (0.3 mol% based on the enone) in 40 ml of benzene. The silyl ether produced was methanolyzed, and GLC analysis using n-octadecane as internal standard revealed that carveol was produced in 98% yield: *trans*-(5*R*,1*S*)/*cis*-(5*R*,1*R*) = 77.4/22.6. The reaction mixture was submitted to a short column chromatography on silica gel, and the n-hexane-ether eluate was distilled under reduced pressure to give 2.63 g (87% yield) of carveol: b.p. 76°C/0.15 Torr, $[\alpha]_D^{20}$ −169.1° (neat). The *trans/cis* ratio of the carveol thus obtained was 77.1/22.9 based on GLC analysis.

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